

NDA 20-388/S011

AUG 25 2000

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Attention: Mama Doucette
Product Director Regulatory Affairs

Dear Ms. Doucette:

Please refer to your supplemental new drug application dated July 31, 2000, received August August 1,2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Navelbine (vinorelbine tartrate) Injection, 10 mg and 50 mg vials.

This "Changes Being Effected" supplemental new drug application provides a response to our May 12,2000 approval letter requesting a new "Changes Being Effected" supplement with final printed labeling containing the following revision:

The fourth paragraph of the WARNINGS section has been revised to read: "Reported cases of interstitial pulmonary changes and ARDS, most of which were fatal, occurred in patients treated with single-agent NAVELBINE. The mean time to onset of these symptoms after vinorelbine administration was 1 week (range 3 to 8 days). Patients with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly."

We note that you have conducted our requested literature search regarding the CYP3A4 metabolism based on drug-drug interactions in order to update the labeling of NAVELBINE. You also searched the Glaxo Wellcome and Pierre Fabre databases for reports. However, your search did not identify any new data. Additionally, you commit to notifying the Division should the review and analysis of data from Pierre Fabre's recent in vitro metabolism studies suggest otherwise.

Additionally, we acknowledge that, as agreed in our June 23,2000 facsimile transmission, we no longer require the insertion of "See Warnings" under PRECAUTIONS: General" since all the pulmonary information and references to pulmonary toxicities were moved from "PRECAUTIONS" to "Warnings".

NDA 20-388 / S-011

Page 2

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 31,2000). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5768.

NAVELBINE®

(vinorelbine tartrate)
Injection

WARNING: NAVELBINE (vinorelbine tartrate) Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for intravenous (IV) use only. Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "WARNING – FOR IV USE ONLY. FATAL if given intrathecally."

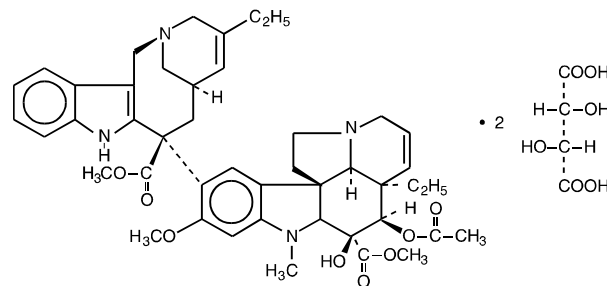
Severe granulocytopenia resulting in increased susceptibility to infection may occur. Granulocyte counts should be ≥ 1000 cells/mm³ prior to the administration of NAVELBINE. The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment.

Caution - It is extremely important that the intravenous needle or catheter be properly positioned before NAVELBINE is injected. Administration of NAVELBINE may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION: Administration Precautions).

DESCRIPTION: NAVELBINE (vinorelbine tartrate) Injection is for intravenous administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in Water for Injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic.

Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincal leukoblastine [*R*-(*R**,*R**)-2,3-dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate has the following structure:



Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is >1000 mg/mL in distilled water. The pH of NAVELBINE Injection is approximately 3.5.

CLINICAL PHARMACOLOGY: Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca^{++} -transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 μ M), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 μ M, but vinblastine and vinorelbine did not have this effect until concentrations of 30 μ M and 40 μ M, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

NAVELBINE® (vinorelbine tartrate) Injection

Pharmacokinetics: The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m² in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/h per kg. Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg.

Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234 to 1169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration to humans. Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans, and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of NAVELBINE (30 mg/m²) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes (see PRECAUTIONS). The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in the feces, respectively. Incomplete recovery in humans is consistent with results in animals where recovery is incomplete, even after prolonged sampling times. A separate study of the urinary excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ± 0.7% of a 30-mg/m² intravenous dose was excreted unchanged in the urine.

The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥60 years and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance), $t_{1/2}$ (the terminal phase half-life), and V_z (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine 30 mg/m² intravenously. CL, V_{ss} , and $t_{1/2}$ were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure ($AUC_{0-\infty}$), and hematological toxicity was observed.

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin with NAVELBINE (see PRECAUTIONS: Drug Interactions).

Clinical Trials: Data from 2 controlled clinical studies (823 patients), as well as additional data from more than 100 patients enrolled in 2 uncontrolled clinical trials, support the use of NAVELBINE in patients with advanced nonsmall cell lung cancer (NSCLC). In a large European clinical trial, 612 patients with Stage III or IV NSCLC, no prior chemotherapy, and WHO Performance Status of 0, 1, or 2 were randomized to treatment with single-agent NAVELBINE (30 mg/m² per week), NAVELBINE (30 mg/m² per week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks), and vindesine (3 mg/m² per week for 7 weeks, then every

NAVELBINE® (vinorelbine tartrate) Injection

other week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks). NAVELBINE plus cisplatin produced longer survival times than vindesine plus cisplatin (median survival 40 weeks versus 32 weeks, $P = 0.03$). The median survival time for patients receiving single-agent NAVELBINE was similar to that observed with vindesine plus cisplatin (31 weeks versus 32 weeks). The 1-year survival rates were 35% for NAVELBINE plus cisplatin, 27% for vindesine plus cisplatin, and 30% for single-agent NAVELBINE. The overall objective response rate (all partial responses) was significantly higher in the patients treated with NAVELBINE plus cisplatin (28%) than in those treated with vindesine plus cisplatin (19%, $P = 0.03$) and in those treated with single-agent NAVELBINE (14%, $P < 0.001$). The response rates reported for vindesine plus cisplatin and single-agent NAVELBINE were not significantly different. Significantly less nausea, vomiting, alopecia, and neurotoxicity were observed in patients receiving single-agent NAVELBINE compared to those receiving the combination of vindesine and cisplatin.

Single-agent NAVELBINE was studied in a North American, randomized clinical trial in which patients with Stage IV NSCLC, no prior chemotherapy, and Karnofsky Performance Status ≥ 70 were treated with NAVELBINE (30 mg/m²) weekly or 5-fluorouracil (5-FU) (425 mg/m² IV bolus) plus leucovorin (LV) (20 mg/m² IV bolus) daily for 5 days every 4 weeks. A total of 211 patients were randomized at a 2:1 ratio to NAVELBINE (143) or 5-FU/LV (68). NAVELBINE showed improved survival time compared to 5-FU/LV. In an intent-to-treat analysis, the median survival time for patients receiving NAVELBINE was 30 weeks and for those receiving 5-FU/LV was 22 weeks ($P = 0.06$). The 1-year survival rates were 24% ($\pm 4\%$ SE) for NAVELBINE and 16% ($\pm 5\%$ SE) for the 5-FU/LV group, using the Kaplan-Meier product-limit estimates. The median survival time with 5-FU/LV was similar to, or slightly better than, that usually observed in untreated patients with advanced NSCLC, suggesting that the difference was not related to some unknown detrimental effect of 5-FU/LV therapy. The response rates (all partial responses) for NAVELBINE and 5-FU/LV were 12% and 3%, respectively. Quality of life (QOL) was also an endpoint in this study. Patients completed a modified Southwest Oncology Group QOL questionnaire which assessed the domains of role functioning, physical functioning, symptom distress, and global QOL. Quality of life was not adversely affected by NAVELBINE when compared to control.

A dose-ranging study of NAVELBINE (20, 25, or 30 mg/m² per week) plus cisplatin (120 mg/m² days 1 and 29, then every 6 weeks) in 32 patients with NSCLC demonstrated a median survival of 44 weeks. There were no responses at the lowest dose level; the response rate was 33% in the 21 patients treated at the 2 highest dose levels.

INDICATIONS AND USAGE: NAVELBINE is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced nonsmall cell lung cancer (NSCLC). In patients with Stage IV NSCLC, NAVELBINE is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, NAVELBINE is indicated in combination with cisplatin.

CONTRAINDICATIONS: Administration of NAVELBINE is contraindicated in patients with pretreatment granulocyte counts < 1000 cells/mm³ (see WARNINGS).

WARNINGS: NAVELBINE should be administered in carefully adjusted doses by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Patients treated with NAVELBINE should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of NAVELBINE. NAVELBINE should not be administered to patients with granulocyte counts < 1000 cells/mm³. Patients

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developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION for recommended dose adjustments for granulocytopenia.

Acute shortness of breath and severe bronchospasm have been reported infrequently, following the administration of NAVELBINE and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is pre-existing pulmonary dysfunction.

Reported cases of interstitial pulmonary changes and ARDS, most of which were fatal, occurred in patients treated with single-agent NAVELBINE. The mean time to onset of these symptoms after vinorelbine administration was 1 week (range 3 to 8 days). Patients with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly.

NAVELBINE has been reported to cause severe constipation (e.g., grade 3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation. Some events have been fatal.

Pregnancy: Pregnancy Category D. NAVELBINE may cause fetal harm if administered to a pregnant woman. A single dose of vinorelbine has been shown to be embryo- and/or fetotoxic in mice and rabbits at doses of 9 mg/m² and 5.5 mg/m², respectively (one third and one sixth the human dose). At nonmaternotoxic doses, fetal weight was reduced and ossification was delayed. There are no studies in pregnant women. If NAVELBINE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with NAVELBINE.

PRECAUTIONS:

General: Most drug-related adverse events of NAVELBINE are reversible. If severe adverse events occur, NAVELBINE should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with NAVELBINE should be carried out with caution and alertness as to possible recurrence of toxicity.

NAVELBINE should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see DOSAGE AND ADMINISTRATION).

Administration of NAVELBINE to patients with prior radiation therapy may result in radiation recall reactions (see ADVERSE REACTIONS and Drug Interactions).

Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving NAVELBINE.

Care must be taken to avoid contamination of the eye with concentrations of NAVELBINE used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

Information for Patients: Patients should be informed that the major acute toxicities of NAVELBINE are related to bone marrow toxicity, specifically granulocytopenia with increased susceptibility to infection. They should be advised to report fever or chills immediately. Women of childbearing potential should be advised to avoid becoming pregnant during treatment. Patients should be advised to contact their physician if they experience increased shortness of breath, cough, or other new pulmonary symptoms, or if they experience symptoms of abdominal pain or constipation.

Laboratory Tests: Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of NAVELBINE (see ADVERSE REACTIONS: Hematologic).

Hepatic: There is no evidence that the toxicity of NAVELBINE is enhanced in patients with elevated liver enzymes. No data are available for patients with severe baseline cholestasis, but the liver plays an important

NAVELBINE® (vinorelbine tartrate) Injection

role in the metabolism of NAVELBINE. Because clinical experience in patients with severe liver disease is limited, caution should be exercised when administering NAVELBINE to patients with severe hepatic injury or impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Acute pulmonary reactions have been reported with NAVELBINE and other anticancer vinca alkaloids used in conjunction with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of granulocytopenia with NAVELBINE used in combination with cisplatin is significantly higher than with single-agent NAVELBINE. Patients who receive NAVELBINE and paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Administration of NAVELBINE to patients with prior or concomitant radiation therapy may result in radiosensitizing effects.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinorelbine tartrate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of NAVELBINE has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown. Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m², approximately one third the human dose) or alternate-day schedule (4.2 mg/m², approximately one seventh the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m² (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NAVELBINE, it is recommended that nursing be discontinued in women who are receiving therapy with NAVELBINE.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in North American clinical studies of IV NAVELBINE, approximately one third were 65 years of age or greater. No overall differences in effectiveness or safety were observed between these patients and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of vinorelbine in elderly and younger adult patients are similar (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: Granulocytopenia is the major dose-limiting toxicity with NAVELBINE. Dose adjustments are required for hematologic toxicity and hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

Data in the following table are based on the experience of 365 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV NAVELBINE as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m² NAVELBINE on a weekly basis.

NAVELBINE® (vinorelbine tartrate) Injection

Table 1: Summary of Adverse Events in 365 Patients Receiving Single-Agent NAVELBINE^{*†}

Adverse Event		All Patients (n = 365)	NSCLC (n = 143)
Bone Marrow			
Granulocytopenia	<2000 cells/mm ³	90%	80%
	<500 cells/mm ³	36%	29%
Leukopenia	<4000 cells/mm ³	92%	81%
	<1000 cells/mm ³	15%	12%
Thrombocytopenia	<100,000 cells/mm ³	5%	4%
	<50,000 cells/mm ³	1%	1%
Anemia	<11 g/dL	83%	77%
	<8 g/dL	9%	1%
Hospitalizations due to granulocytopenic complications		9%	8%

Adverse Event	All Grades		Grade 3		Grade 4	
	All Patients	NSCLC	All Patients	NSCLC	All Patients	NSCLC
Clinical Chemistry Elevations						
Total Bilirubin (n = 351)	13%	9%	4%	3%	3%	2%
SGOT (n = 346)	67%	54%	5%	2%	1%	1%
General						
Asthenia	36%	27%	7%	5%	0%	0%
Injection Site Reactions	28%	38%	2%	5%	0%	0%
Injection Site Pain	16%	13%	2%	1%	0%	0%
Phlebitis	7%	10%	<1%	1%	0%	0%
Digestive						
Nausea	44%	34%	2%	1%	0%	0%
Vomiting	20%	15%	2%	1%	0%	0%
Constipation	35%	29%	3%	2%	0%	0%
Diarrhea	17%	13%	1%	1%	0%	0%
Peripheral Neuropathy [‡]	25%	20%	1%	1%	<1%	0%
Dyspnea	7%	3%	2%	2%	1%	0%
Alopecia	12%	12%	≤1%	1%	0%	0%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.

† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.

‡ Incidence of paresthesia plus hypesthesia.

NAVELBINE® (vinorelbine tartrate) Injection

Hematologic: Granulocytopenia was the major dose-limiting toxicity with NAVELBINE; it was generally reversible and not cumulative over time. Granulocyte nadirs occurred 7 to 10 days after the dose, with granulocyte recovery usually within the following 7 to 14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of patients. Septic deaths occurred in approximately 1% of patients. Prophylactic hematologic growth factors have not been routinely used with NAVELBINE. If medically necessary, growth factors may be administered at recommended doses no earlier than 24 hours after the administration of cytotoxic chemotherapy. Growth factors should not be administered in the period 24 hours before the administration of chemotherapy.

Grade 3 or 4 anemia occurred in 1% of patients, although blood products were administered to 18% of patients who received NAVELBINE. Grade 3 or 4 thrombocytopenia was reported in 1% of patients.

Neurologic: Mild to moderate peripheral neuropathy manifested by paresthesia and hypesthesia were the most frequently reported neurologic toxicities. Loss of deep tendon reflexes occurred in less than 5% of patients. The development of severe peripheral neuropathy was infrequent (1%) and generally reversible.

Skin: Alopecia was reported in 12% of patients and was usually mild.

Like other anticancer vinca alkaloids, NAVELBINE is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately one third of patients; 5% were severe. Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients.

Gastrointestinal: Mild or moderate nausea occurred in 34% of patients treated with NAVELBINE; severe nausea was infrequent (<2%). Prophylactic administration of antiemetics was not routine in patients treated with single-agent NAVELBINE. Due to the low incidence of severe nausea and vomiting with single-agent NAVELBINE, the use of serotonin antagonists is generally not required. Constipation occurred in 29% of patients, with paralytic ileus occurring in 1%. Vomiting, diarrhea, anorexia, and stomatitis were usually mild or moderate and each occurred in less than 20% of patients.

Hepatic: Transient elevations of liver enzymes were reported without clinical symptoms.

Cardiovascular: Chest pain was reported in 5% of patients. Most reports of chest pain were in patients who had either a history of cardiovascular disease or tumor within the chest. There have been rare reports of myocardial infarction.

Pulmonary: Shortness of breath was reported in 3% of patients; it was severe in 2% (see WARNINGS). Interstitial pulmonary changes were documented.

Other: Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing.

Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia, arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.

Combination Use: In a randomized study, 206 patients received treatment with NAVELBINE plus cisplatin and 206 patients received single-agent NAVELBINE. The toxicity profile of cisplatin is known (see full prescribing information for cisplatin). The incidence of severe nausea and vomiting was 30% for NAVELBINE/cisplatin compared to <2% for single-agent NAVELBINE. Cisplatin did not appear to increase the incidence of neurotoxicity observed with single-agent NAVELBINE. However, myelosuppression, specifically Grade 3 and 4 granulocytopenia, was greater with the combination of NAVELBINE/cisplatin (79%) than with single-agent NAVELBINE (53%). The incidence of fever and infection may be increased with the combination.

Observed During Clinical Practice: In addition to the adverse events reported from clinical trials, the following events have been identified during post-approval use of NAVELBINE. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have

NAVELBINE® (vinorelbine tartrate) Injection

been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to NAVELBINE.

Body as a Whole: Systemic allergic reactions reported as anaphylaxis, pruritus, urticaria, and angioedema; flushing; and radiation recall events such as dermatitis and esophagitis (see PRECAUTIONS) have been reported.

Hematologic: Thromboembolic events, including pulmonary embolus and deep venous thrombosis, have been reported primarily in seriously ill and debilitated patients with known predisposing risk factors for these events.

Neurologic: Peripheral neurotoxicities such as, but not limited to, muscle weakness and disturbance of gait, have been observed in patients with and without prior symptoms. There may be increased potential for neurotoxicity in patients with pre-existing neuropathy, regardless of etiology, who receive NAVELBINE. Vestibular and auditory deficits have been observed with NAVELBINE, usually when used in combination with cisplatin.

Skin: Injection site reactions, including localized rash and urticaria, blister formation, and skin sloughing have been observed in clinical practice. Some of these reactions may be delayed in appearance.

Gastrointestinal: Dysphagia and mucositis have been reported.

Cardiovascular: Hypertension, hypotension, vasodilation, tachycardia, and pulmonary edema have been reported.

Pulmonary: Pneumonia has been reported.

Musculoskeletal: Headache has been reported, with and without other musculoskeletal aches and pains.

Other: Pain in tumor-containing tissue, back pain, and abdominal pain have been reported. Electrolyte abnormalities, including hyponatremia with or without the syndrome of inappropriate ADH secretion, have been reported in seriously ill and debilitated patients.

Combination Use: Patients with prior exposure to paclitaxel and who have demonstrated neuropathy should be monitored closely for new or worsening neuropathy. Patients who have experienced neuropathy with previous drug regimens should be monitored for symptoms of neuropathy while receiving NAVELBINE. NAVELBINE may result in radiosensitizing effects with prior or concomitant radiation therapy (see PRECAUTIONS).

OVERDOSAGE: There is no known antidote for overdoses of NAVELBINE. Overdoses involving quantities up to 10 times the recommended dose (30 mg/m^2) have been reported. The toxicities described were consistent with those listed in the ADVERSE REACTIONS section including paralytic ileus, stomatitis, and esophagitis. Bone marrow aplasia, sepsis, and paresis have also been reported. Fatalities have occurred following overdose of NAVELBINE. If overdosage occurs, general supportive measures together with appropriate blood transfusions, growth factors, and antibiotics should be instituted as deemed necessary by the physician.

DOSAGE AND ADMINISTRATION: The usual initial dose of NAVELBINE is 30 mg/m^2 administered weekly. The recommended method of administration is an intravenous injection over 6 to 10 minutes. In controlled trials, single-agent NAVELBINE was given weekly until progression or dose-limiting toxicity. NAVELBINE was used at the same dose in combination with 120 mg/m^2 of cisplatin, given on days 1 and 29, then every 6 weeks.

No dose adjustments are required for renal insufficiency. If moderate or severe neurotoxicity develops, NAVELBINE should be discontinued. The dosage should be adjusted according to hematologic toxicity or hepatic insufficiency, whichever results in the lower dose.

NAVELBINE® (vinorelbine tartrate) Injection

Dose Modifications for Hematologic Toxicity: Granulocyte counts should be ≥ 1000 cells/mm³ prior to the administration of NAVELBINE. Adjustments in the dosage of NAVELBINE should be based on granulocyte counts obtained on the day of treatment according to Table 2.

Table 2: Dose Adjustments Based on Granulocyte Counts

Granulocytes (cells/mm ³) on Days of Treatment	Dose of NAVELBINE (mg/m ²)
≥ 1500	30
1000 to 1499	15
<1000	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is <1000 cells/mm ³ , discontinue NAVELBINE.
Note: For patients who, during treatment with NAVELBINE, have experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of NAVELBINE should be: 22.5 mg/m ² for granulocytes ≥ 1500 cells/mm ³ 11.25 mg/m ² for granulocytes 1000 to 1499 cells/mm ³	

Dose Modification for Hepatic Insufficiency: NAVELBINE should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with NAVELBINE, the dose should be adjusted for total bilirubin according to Table 3.

Table 3: Dose Modification Based on Total Bilirubin

Total Bilirubin (mg/dL)	Dose of NAVELBINE (mg/m ²)
≤ 2.0	30
2.1 to 3.0	15
>3.0	7.5

Dose Modification for Concurrent Hematologic Toxicity and Hepatic Insufficiency: In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses determined from Table 2 and Table 3 should be administered.

Administration Precautions: Caution - NAVELBINE must be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any NAVELBINE is injected. Leakage into surrounding tissue during intravenous administration of NAVELBINE may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with NAVELBINE, institutional guidelines may be used. The *ONS Chemotherapy Guidelines* provide additional recommendations for the prevention of extravasation injuries.¹

As with other toxic compounds, caution should be exercised in handling and preparing the solution of NAVELBINE. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of NAVELBINE contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with

NAVELBINE® (vinorelbine tartrate) Injection

another vinca alkaloid. If this happens with NAVELBINE, the eye should be flushed with water immediately and thoroughly.

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.²⁻⁸ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

NAVELBINE Injection is a clear, colorless to pale yellow solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, NAVELBINE should not be administered.

Preparation for Administration: NAVELBINE Injection must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted NAVELBINE should be administered over 6 to 10 minutes into the side port of a free-flowing IV **closest to the IV bag** followed by flushing with at least 75 to 125 mL of one of the solutions. Diluted NAVELBINE may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5° to 30°C (41° to 86°F).

Syringe: The calculated dose of NAVELBINE should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution:

5% Dextrose Injection, USP

0.9% Sodium Chloride Injection, USP

IV Bag: The calculated dose of NAVELBINE should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution:

5% Dextrose Injection, USP

0.9% Sodium Chloride Injection, USP

0.45% Sodium Chloride Injection, USP

5% Dextrose and 0.45% Sodium Chloride Injection, USP

Ringer's Injection, USP

Lactated Ringer's Injection, USP

Stability: Unopened vials of NAVELBINE are stable until the date indicated on the package when stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton. Unopened vials of NAVELBINE are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product should not be frozen.

HOW SUPPLIED: NAVELBINE Injection is a clear, colorless to pale yellow solution in Water for Injection, containing 10 mg vinorelbine per mL. NAVELBINE Injection is available in single-use, clear glass vials with elastomeric stoppers and royal blue caps, individually packaged in a carton in the following vial sizes:

10 mg/1 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-01).

50 mg/5 mL Single-Use Vial, Carton of 1 (NDC 0173-0656-44).

Store the vials under refrigeration at 2° to 8°C (36° to 46°F) in the carton. Protect from light. DO NOT FREEZE.

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